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Abstract: Because of the lack of curative approaches for most patients with malignant brain tumors, supportive therapy, which aims at maintaining quality of life and functional independence, has a central role in the treatment of many patients. Steroids are particularly important in the setting of supportive therapy. They are commonly used to treat tumor-associated edema, and their administration is typically associated with rapid symptom relief, such as the resolution of headaches. Besides their antiedema activity, corticosteroids are characterized by their potent antilymphoma properties and their effects against acute or delayed emesis caused by systemic chemotherapy in cancer patients. Accordingly, steroids are among the most frequently used drugs in oncology. These desirable properties of steroids are counterbalanced by cardiovascular, muscular, and psychiatric side effects. On the cellular level, corticosteroids exert various effects that translate into the desired clinical activity, but they also evoke significant toxicity that may outweigh the beneficial effects. The mode of action and the limitations of steroid treatment are summarized in this review article. Interactions between steroids and other drugs must be considered. A particular challenge to the ongoing use of glucocorticoids is that newer therapeutic approaches are being introduced in neuro-oncology for which concomitant steroids are likely to be contraindicated. These include the emergence of various immunotherapeutic approaches including vaccination strategies and treatment with immune checkpoint inhibitors. Since the administration of steroids may interfere with the activity of these novel therapies, an even more critical evaluation of their use will be required.

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Corticosteroid use in Neuro-Oncology: an update

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Abstract

Because of the lack of curative approaches for most patients with malignant brain tumors, supportive therapy which aims at maintaining quality of life and functional independence has a central role in the treatment of many patients. Here, steroids play a central role: they are commonly used to treat tumor-associated edema and their administration is typically associated with rapid symptom relief such as the resolution of headaches. Beside their anti-edema activity, corticosteroids are characterized by their potent anti-lymphoma properties and their effects against acute or delayed emesis caused by systemic chemotherapy in cancer patients. Accordingly, steroids are among the most frequently used drugs in oncology, not only in patients with brain tumors. These desirable properties of steroids are counterbalanced by cardiovascular, muscular and psychiatric side effects. On the cellular level, corticosteroids exert various effects which translate into the desired clinical activity but also evoke significant toxicity which may outweigh the beneficial effects. The mode of action and the limitations of steroid treatment are summarized in this review article. Interactions between steroids and other drugs must be considered. A particular challenge to the ongoing use of glucocorticoids is that fact that newer therapeutic approaches are being introduced in neuro-oncology for which concomitant steroids are likely to be contraindicated. These include the emergence of various immunotherapeutic approaches including vaccination strategies and treatment with immune checkpoint inhibitors. Since the administration of steroids may interfere with the activity of these novel therapies, an even more critical evaluation of their use will be required.

Background

Corticosteroids are a class of biological mediators produced within the adrenal gland and synthesized from cholesterol. They are involved in the regulation of various processes such as metabolism, electrolyte regulation, inflammation and stress responses. Based on their major effects they are divided into different groups including glucocorticoids and mineralocorticoids. Cortisol is the most prominent physiological mediator exerting glucocorticoid effects in humans, aldosterone is the hormone with the strongest mineralocorticoid activity. Chemical modifications of the naturally occurring steroid hormones resulted in the generation of numerous synthetic corticosteroids within the last decades. Since then, these drugs have played a prominent role in the treatment of various pathological conditions and diseases. The gluco- and mineralocorticoid activity of these synthetic drugs varies significantly. Accordingly, choosing the appropriate compound requires anticipation of the desired effect but also careful consideration of potential side effects.

As outlined below in more detail, steroids are administered to brain tumor patients mainly to (i) reduce the tumor-surrounding edema and thereby the mass effect in the brain, (ii) target lymphomas in the CNS and (iii) prevent or treat chemotherapy-induced nausea and vomiting. These effects are mediated by the glucocorticoid activity of steroids. The glucocorticoid and mineralocorticoid potency of some frequently administered corticosteroids are summarized in Table 1. The available compounds differ significantly in their duration of action. Because of its long half-life, which allows for administration of a single daily dose, dexamethasone has been the favourite drug for most indications. Furthermore, its strong glucocorticoid potency associated with virtually absent mineralocorticoid effects reduces the risk of electrolyte imbalances.

Mode of action

Glucocorticoids interact with the glucocorticoid receptor (GR) which is encoded by a gene located on chromosome 5 [1]. The expression of the GR gene is under the control of at least 3 promoters which allows for tissue-specific GR expression [2]. Because of alternative splicing as well as post-transcriptional and post-translational modifications, multiple GR isoforms exist [3]. The GR contains DNA-binding and ligand-binding domains [4]. It binds to several other proteins including heat shock protein 90 which interacts with the ligand-binding domain and thereby maintains the receptor in an inactive state [5]. Activation of the GR requires binding of a ligand which results in GR hyperphosphorylation and translation into the nucleus. The transcriptional effects of the GR are mediated through interaction of its DNA-binding domain with glucocorticoid-responsive elements (GRE) which are specific DNA sequences. The transcriptional activity of the GR is conferred by additional co-activators which comprise a group of proteins that induce conformational changes in the GR which promote GR-mediated transcriptional activation [6]. Still, it has not been fully understood how a receptor such as the GR can mediate a variety of different effects on the cellular level. Ligand binding to the GR can result in a direct induction or repression of target gene expression. Furthermore, steroid-mediated induction of transcription factor expression controls numerous additional genes which contributes in an indirect manner to the multitude of steroid-exerted effects [7].
The clinical application of synthetic steroids, e.g. their use for the treatment of brain tumor edema or their anti-lymphoma activity, is frequently limited by their diminishing effect over time. The underlying mechanisms which preclude durable responses to steroids have been largely unknown. On the cellular level, the administration of drugs which act as agonists on the GR induces a down-regulation of GR expression [8,9], an effect which is mediated by reduced GR transcription, decreased half-life of GR mRNA and reduced stability of the GR protein [10,11]. Together with other cellular processes, these mechanisms may contribute to the

development of resistance to steroid treatment in different conditions. Steroids are finally metabolized in the liver in a cytochrome P450-dependent manner [12]. Combined administration of drugs which act as P450 inducers such as the anticonvulsant phenytoin, which is still commonly used, may therefore alter the turnover of glucocorticoids and reduce their bioavailability [13,14].

Indications for the use of steroids

Anti-edema activity

The striking anti-edema effects of steroids have been recognized several decades ago [15]. Since then, glucocorticoids have been used for various conditions where a reduction of the intracranial pressure due to a peritumoral fluid collection must be achieved. Accordingly, steroids are commonly applied in a prophylactic manner perioperatively, during radiation therapy and whenever rapid relief from clinical symptoms due to mass effect in the brain is required [16,17]. Steroids modulate the permeability of the blood brain barrier (BBB) which is frequently compromised in brain tumors because both benign and malignant brain tumors secrete various cytokines such as *vascular endothelial growth factor* (VEGF) which act on endothelial cells located within or around the tumor. Although edema is most commonly found in patients with malignant lesions such as high-grade gliomas or metastases, it can also increase the mass effect of benign tumors such as meningiomas [18,19]. The effects of glucocorticoids on the BBB are mediated through various genes and molecules including claudins, occludin, zona occludens (ZO)-1 and vascular endothelial (VE)-cadherin which influence endothelial permeability. Steroid administration decreases the permeability of the BBB and limit the extravasation of fluid [20,21]. Similar to other steroid effects, the anti-edema activity is temporary. Even in the context of scenarios with ongoing anti-edema benefits, sustained administration of steroids can impair quality of life because of severe side effects (see below).

Treatment of lymphomatous neoplasms

Primary CNS lymphomas (PCNSL) or secondary lymphomatous neoplasms of the brain typically respond quickly upon administration of steroids which can induce cell cycle arrest and cell death, mostly apoptosis in a p38 mitogen-activated protein kinase (MAPK)-dependent manner, in B and T cells [17,22,23]. Accordingly, various treatment regimens for lymphomas comprise steroids, at least in the beginning of the treatment when rapid effects are required. However, steroid effects against lymphomas are transient and the tumor recurs in virtually all patients unless a chemotherapeutic regimen or irradiation are applied [24]. When a lymphoma is suspected, the administration of steroids should be avoided to allow for a histopathological confirmation of the diagnosis. Still, even in patients who have already been exposed to steroids, the diagnosis may be established successfully [25]. Furthermore, rapid clinical and radiographic responses to steroid administration are not restricted to lymphomas but can also be observed in patients suffering from inflammatory conditions. The situation is different in tumor entities other than lymphomas. There is no clinical evidence that steroids inhibit the growth of gliomas or metastases in human patients. However, data from preclinical studies suggest that the proliferation of some glioma cells is reduced upon exposure to dexamethasone [26]. This is at odds with other reports which claim that steroids have no effect or even stimulate the growth of glioma cells [27,28]. Furthermore, there are concerns which are largely based on preclinical findings, that the administration of glucocorticoids renders tumor cells resistant to chemotherapy [29-31]. It remains to be determined whether steroid intake truly interferes with the efficacy of chemotherapy in human patients *in vivo*. However, because of this concern, steroid administration in cancer patients should always be critically evaluated.

Anti-emetic properties

Cancer patients receiving systemic chemotherapy are frequently affected by severe nausea and vomiting. Chemotherapy-induced nausea and vomiting (CINV) can severely impair quality of life and induce further complications such as dehydration and electrolyte disturbances. Various drugs including the widely used 5-HT_3 receptor antagonists and the neurokinin (NK)-1 receptor antagonist aprepitant are available for the prophylaxis and treatment of CINV. Corticosteroids such as methylprednisolone and dexamethasone have also been used as antiemetic agents for decades [32]. Similar to other steroid-mediated effects, the receptors and pathways which contribute to these effects have only partially been understood. Reduced release of 5-HT_3 from blood cells upon administration of steroids as well as direct effects on cellular 5-HT_3 receptor expression have been suggested as important factors [33,34]. Furthermore, preclinical data point to a direct effect of corticosteroids in the medulla oblongata [35]. Steroids are administered either alone or in combination with other drugs. The combination of a 5-HT_3 receptor antagonist, aprepitant, and dexamethasone has been recommended for the prophylaxis of patients treated with moderately or highly emetogenic chemotherapy and therefore at high risk of developing CINV [36]. Recent data from a randomized double-blind study indicate that dexamethasone and aprepitant have similar activity in preventing emesis in breast cancer patients receiving a chemotherapy regimen containing anthracyclines plus cyclophosphamide [37]. Furthermore, there was no significant difference in the toxicity profile of the 2 antiemetic regimens used in this trial. Accordingly, the value of steroids in the prophylaxis and treatment of CINV remains undisputed and their use as single agents may be sufficient in some patients.

Dosing and tapering

The vast majority of patients suffering from brain tumors will receive steroids at some point in time during the course of their disease [38]. Although various synthetic glucocorticoids are available, dexamethasone is by far the most frequently used compound, most likely because of its properties described above [39]. In sharp contrast to the widespread use of glucocorticoids in brain cancer patients, there is hardly any evidence from clinical trials guiding choice of optimal dose, duration of treatment and tapering schemes. A randomized trial assessed the activity of 8 mg dexamethasone versus 16 mg dexamethasone or 4 mg versus 16 mg in patients with brain metastases. A similar improvement of the Karnofsky performance status (KPS) was observed in all groups. However, side effects were significantly more frequent in patients treated with 16 mg dexamethasone per day [40]. Whether the dose of glucocorticoids should be based on bodyweight or body surface has not been examined either. Furthermore, it remains unclear whether elderly patients should receive lower doses than younger patients because of an increased risk of side effects and potentially less susceptibility to the development of severely increased intracranial pressure. Finally, it remains doubtful whether doses higher than 16 mg dexamethasone per day provide additional beneficial effect [41]. Attempts to define a standard regimen for steroid application have largely failed which means that the dose must be adapted to each patient's individual needs [38]. Not surprisingly, considerable variations in the administration and prescribing practice of steroids have been observed [42]. Because of steroid-associated toxicity, tapering should be considered as soon as clinically acceptable [43]. Although reliable data are lacking, it must be assumed that many patients receive steroids too long and at a higher dose than necessary [42,44]. Steroids can be stopped quickly in patients who were taking them for a short period of time, that is, typically no longer than 10-14 days. In contrast, prolonged administration for weeks or months requires careful tapering over a longer period of time to avoid clinical deterioration because of manifest hypocortisolism due to suppression of adrenal function. To exclude the latter, basal cortisol levels in the morning may be determined at the end of tapering before the administration is stopped. Patients with insufficient cortisol levels can benefit from substitution with hydrocortisone, typically administered in 2 doses in the morning and at noon to mimic the physiological secretion of the hormone. In the absence of particular high cortisol needs, 20 mg in the morning and 10 mg at noon or early afternoon are sufficient for most patients [45].

Side effects and toxicity

Depending on the type and the dose of the administered steroid, side effects can occur in different ranges of severity. While some of these undesired effects only develop over time, others can manifest within days of the first steroid intake. Most of the symptoms are manageable; still, some side effects can be fatal when not recognized.

One of the most common side effects of steroid exposure is arterial hypertension, occurring in at least 20% of patients treated with steroids in a dose-dependent manner [46]. This increase in systolic blood pressure is usually reversible, and cessation of steroid intake usually normalizes blood pressure again. If stopping medication is not an option in the context of the disease, symptomatic treatment of hypertension must be established, preferentially with diuretics, as hypervolemia induced by steroids is a main cause of hypertension in these patients.

Another relevant side effect of steroid use is the negative impact on the immune system, leading to a higher susceptibility to fungal infections, such as candidiasis and pneumocystis jirovecii pneumonia (PJP) [47]. In high-risk patients with an impaired immune system, such as patients after organ transplantation or patients undergoing chemo- or radiotherapy, prophylactic treatment for PJP involving trimethoprim-sulfamethoxazole should be evaluated if prolonged steroid exposure is deemed necessary [48].

Side effects that occur mainly in the long-term course of steroid exposure, but should be considered early to avoid morbidity, are, among others, osteoporosis and steroid-induced diabetes. Glucocorticoid-induced osteoporosis is the most common form of iatrogenic osteoporosis, and may occur in up to 50% of steroid-treated patients [49,50]. It involves an increased risk in fractures with more than 5-fold increased risks of hip or vertebral fractures [51,52], which are associated with higher morbidity and mortality. The use of bisphosphonates should be evaluated, and vitamin D and calcium should be supplemented at doses of 800 IU and 800-1200 mg per day in such patients [53]. In brain tumor patients requiring steroids and antiepileptic medication caution needs to be taken since drugs such as valproic acid or phenytoin may promote osteoporosis, too [54-56]. Replacement of these agents with anticonvulsants with a more suitable toxicity profile should be considered.

Diabetes occurs in up to 50% of steroid-treated patients, and is the most common form of drug-induced diabetes mellitus [57]. Accordingly, blood sugar levels should be determined regularly in patients taking steroids, especially when diabetes preexists. Management of steroid-induced diabetes does not differ from that of regular type-2 diabetes, and patients with repeatedly pathological blood sugar levels should be treated adequately to prevent long-term complications, including cardiovascular and renal damage.

Steroid-induced myopathy has been described in up to 60% of patients taking steroids, caused by decreased protein synthesis and induction of muscle protein catabolism [58]. Two distinct types of steroid-induced myopathy are described: the less common acute form, a generalised myopathy partially associated with rhabdomyolysis, occurring within days after the onset of steroid treatment and often associated with high doses of steroids [59,60]; and the classic form, a chronic myopathy characterized by proximal muscle weakness, that develops over a longer time course after prolonged steroid administration [58,61]. Myopathy may have even more devastating impacts on patients who already have a motor deficit or balance issues relating to their tumor. It has repeatedly been claimed that myopathy occurs more frequently when fluorinated steroids are administered [62-64]. However, compelling evidence from clinical trials comparing fluorinated and non-fluorinated steroids is lacking. Accordingly, due to its long half-life, low mineralocorticoid effects and high glucocorticoid potency, dexamethasone, a fluorinated drug, remains the first choice of steroid in brain tumor patients. Recovery from myopathy after dose reduction or tapering may take months, and physical therapy is recommended to attenuate the symptoms [65].

Psychiatric effects of steroids have been described to occur in up to 60% of patients [66,67], throughout the treatment period, with early symptoms starting within 2 weeks and being most often dose-dependent, such as insomnia, emotional lability, hypomanic and manic episodes, and some in the later course, such as depression [68,69]. These symptoms tend to resolve after cessation of steroid treatment. Meanwhile, neuroleptic drugs, e.g. olanzapine, may be required to ameliorate some of these behavioural sequelae. Finally, steroid intake is associated with an increase in cataracts and the rare occurrence of avascular bone, e.g., hip necrosis. A summary of the most relevant steroid-associated side effects as well as potential prophylactic measures and therapies is provided in Table 2.

Steroids and immunotherapy

Immunotherapy has gained increasing interest in neurooncology within the last years because of the availability of novel agents which are successfully used or currently evaluated in late-stage clinical development in other tumor entities. The emergence of various immunotherapeutic approaches poses a particular challenge for the use of steroids because of their well-known immunosuppressive effects. Steroid-induced lymphopenia increases the risk for opportunistic infections (see above) but may also limit therapeutic approaches which aim at activating the immune system and boost anti-tumor immune responses.

One of these novel immunotherapeutic agents, that is, ipilimumab, targets *cytotoxic T lymphocyte antigen* (CTLA)-4 and interferes with the inhibition of T cell function which subsequently translates into enhanced anti-tumor activity. While the drug has already been registered for the treatment of advanced melanoma [70], current efforts aim at defining the potential activity of ipilimumab in patients with malignant gliomas. Similarly, targeting of the immune cell receptor *programmed cell death* (PD)-1 or its ligand PD-L1 is currently in advanced clinical development [71] and clinical trials combining ipilimumab with the anti-PD-1 antibody nivolumab are currently ongoing in patients with glioblastoma [72].

Another immunotherapeutic concept, vaccination, has also progressed within the last years [73]. Again, steroids may interfere with the boosting of an immune response and therefore be counterproductive in patients who are treated with a vaccine. Accordingly, several vaccination trials restrict the use of steroids at the time of enrolment to select only patients with a suitable immunological “configuration”.

Steroid-sparing drugs

Because of the limited activity of steroids and, even more importantly, the side effects associated with their administration, steroid-sparing drugs may be very welcome. However, convincing alternatives are hardly available. Bevacizumab, which is a VEGF neutralizing antibody, has strong anti-edema activity in the brain [74]. However, approval for this indication is lacking, and cost is a limiting factor at present. The administration of corticorelin acetate, a synthetic analog of human corticotropin-releasing factor (hCRF), to brain tumor patients allowed for a higher maximal reduction of the dexamethasone dose compared to control-treated patients in a randomized trial. Furthermore, patients in the corticorelin acetate group were less likely affected by myopathy and cushingoid appearance [75]. Drugs with uncertain effects on the edema surrounding brain tumors include boswellic acids, cyclooxygenase (COX)-2 inhibitors and angiotensin-II inhibitors (reviewed in [76]).

Conclusion and outlook

The introduction of steroids 60 years ago was a milestone in the treatment of brain tumor patients. Their rapid effect on the tumor-associated edema makes them indispensable even all these decades after their first administration, and steroids remain a mainstay in the management of brain tumors. Despite their widespread use, hardly any data from larger clinical studies exist which precludes definite answers to important questions including the choice of the most appropriate synthetic drug, the most effective dose and the optimal time-point for tapering. Chronic administration of steroids can be associated with severe side effects which must be considered in any patients with regard to quality of life and functional autonomy. Steroid independence should be incorporated as exploratory endpoints in future trials in brain tumor patients as already done in the AVAGLIO trial [77]. A better understanding of the cellular mechanisms mediating the clinical activity of corticosteroids may help to design novel compounds which selectively confer the urgently needed beneficial effects but are no longer associated with detrimental toxicity. In parallel, intense research is needed to find novel strategies which allow for a substitution of steroids by other compounds. The ongoing development and clinical assessment of corticorelin acetate could be a first step towards a reduction of steroids doses and associated side effects . However, a final evaluation of this drug is pending and data from additional trials need to be awaited.

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Table 1. Pharmacological properties of cortisol and synthetic glucocorticoids

	Biological half-life	**Mineralocorticoid potency**	**Glucocorticoid potency**	**Recommended daily dose (range)**	**Cortisol equivalent**	**Cushing threshold**
Cortisol (known as hydrocortisone when used therapeutically)	8-12 h	1	1	- (hydrocortisone: 20-30 mg)	1	30
Cortisone	8-12 h	0.8	0.8	-	1.25	40
Prednisone	12-36 h	0.6	4	5-60 mg	0.25	7.5
Methylprednisolone	12-36 h	-	5	500-1000 mg	0.2	6
Dexamethasone	> 48 h	-	30	2-24 mg	0.04	1.5
Budesonide	n.a.	n.a.	> 30	400-1600 mg	n.a.	n.a.

Table 2. Steroid-associated side effects

Side effects	Frequency[1]	Symptoms	Prophylaxis / Treatment
Cushing's syndrome		Moon face Hyperglycemia Hypertension Striae	P: stay below Cushing threshold (see Table 1) T: tapering steroid dose below Cushing threshold
Osteoporosis	Up to 50%	Pain Fractures	P: short treatment periods T: Calcium and Vitamin D supplement, bisphosphonates
Myopathy	Up to 60%	Muscle weakness	P: stay below 10mg/d prednisone (equivalent) T: switch from fluorinated to non-fluorinated steroids physical therapy
Steroid-induced diabetes	Up to 50%	Cardiovascular alterations Renal failure Visual impairment	P: regular blood sugar samples for early diagnosis T: diabetes mellitus type 2 therapy regimen (including insulin if necessary)
Thrombembolic events	3-fold increased compared to untreated [78,79]	Deep venous thrombosis Pulmonary embolism Stroke	P: compression hosiery, low-dose heparin, mobilisation T: oral anticoagulants or heparin in therapeutic doses
Immunosuppression	30-100%	Opportunistic infections Wound healing problems Ulcerations	P: regular white blood count T: prophylactic or therapeutic trimethoprim-sulfamethoxazole Antibiotics Antacids
Psychiatric disorders	Up to 60%	Insomnia Mood disorders Psychosis	P: stay below 40mg/d prednisone (equivalent) T: neuroleptics, sedatives

Legend to Table 2: P, prophylaxis; T, therapy

[1]upon prolonged use